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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: ;
SHIGERU KAWAHARA ET AL : EXAMINER: ZUCKER
SERIAL NO. : 09/830,159 ;
FILED: JUNE 27, 2001 : GROUP ART UNIT: 1623
FOR: CRYSTALLIZATION :
PROCESSES FOR THE
FORMATION OF STABLE
CRYSTALS OF ASPARTAME
DERIVATIVE

DECLARATION UNDER 37 C.F.R. § 1.132

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Now comes Shigeru Kawahara, who deposes and states:

1. That I am a named inventor of the above-identified application.
2. That I received my degree in chemistry from Tokyo Institute of Technology in 1978.
3. That I have been employed by Ajinomoto Company, Inc., the assignee of the above-identified application for 5 years as chemist in the field of process chemistry.
4. That the following experiments were carried out by me or under my direct supervision and control.

A Substantial Repetition of Example 2 of U.S. Patent No. 5,510,508 (Claude et al):

The following were introduced successively, with stirring, into a reactor equipped with a stirrer capable of ensuring a very good transfer of gaseous hydrogen into the liquid phase: 60 cm³ of a 0.1M aqueous solution of acetic acid, 1g of 10% palladium on activated carbon, 2.55 g of 3,3-dimethylbutyraldehyde, 30 cm³ of methanol, and 5g of aspartame.

After the reactor had been purged with a stream of nitrogen, the mixture was hydrogenated at a relative pressure of 1 bar (0.1MPa) and at room temperature. The progress of the ~~reaction~~ ^{July 14, 2002 SK} was monitored by taking a crude sample and assaying the product formed by high performance liquid chromatography (HPLC). The concentration of desired product was determined by comparison with a calibration curve established beforehand. After a hydrogenation time of 2 hours, the formation of 56% of the expected product was observed.

The reaction was then interrupted by purging the reactor with a stream of nitrogen and removing the catalyst by filtering on a fine filter (0.5 μ m). The methanol was then removed by evaporation under vacuum, the temperature of the water bath being kept at 38-40°C. During the removal of methanol by evaporation under vacuum, the temperature of the mass inside the vessel was checked by a thermometer. After 3-13 minutes, an oily material was generated, and after another 1 minute (14 minutes from starting evaporation), a white solid rapidly precipitated. At that time, the temperature of the mass inside the vessel was 23°C. The mixture was stirred for 4 hours at room temperature in order to complete the precipitation. The product was filtered off, and the resulting wet product, when examined by X-ray powder diffractometry had characteristic X-ray diffraction peaks at least at diffraction angles of 5.1°, 21.1°, 21.3°, and 8.3° (2 θ CuK α rays) and it was determined to be B-type crystals. None of the A-type crystals were observed. The wet product was dried in a vacuum

oven at 40°C (house vacuum) for 16 hours. The dry material, when examined by X-ray power diffractometry, had characteristic X-ray diffraction peaks at least at diffraction angles of 5.6°, 8.4°, 17.1°, and 18.8° (2θ CuKα rays) and it was determined to be amorphous G-type crystals. Then the dry product was washed with 50 cm³ of hexane and dried, 3.1g of N-[N(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester (yield 45%) were finally obtained in the form of a white powder (95% purity by HPLC).

5. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

6. Further Declarant saith not.

Shigeru Kawahara
Shigeru Kawahara

July 19, 2002
Date

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